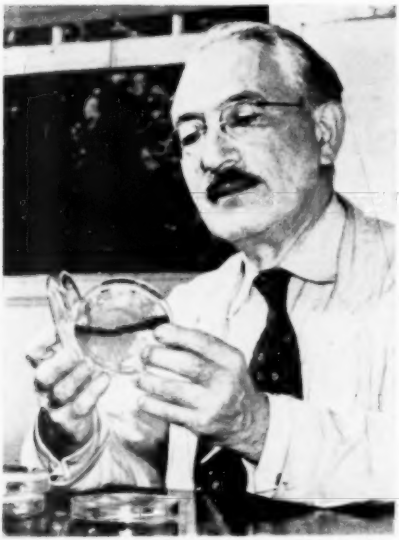
American Journal of Pharmacy

AND THE SCIENCES
SUPPORTING PUBLIC HEALTH



DR. SELMAN WAKSMAN
Nobel Laureate for Discovery of Streptomycin
(See review on tuberculostatic drugs)

Since 1825 *December 1952*

Philadelphia College of Pharmacy and Science

Founded 1821

For well over a century pioneering in Education in the Fields of Pharmacy and the Allied Health Sciences. B.Sc., M.Sc. and D.Sc. degree courses offered. Co-educational. Classes commence each September. Write for catalog and application papers now.

43d Street, Woodland and Kingsessing Avenues

Philadelphia 4, Pa.

American Journal of Pharmacy

Published monthly by the Philadelphia College of Pharmacy and Science
43d Street, Kingsessing and Woodland Avenues, Philadelphia 4, Pa.

Annual Subscription $4.00 — Foreign Postage, 25 Cents Extra
Single Numbers, 40 Cents — Back Numbers, 50 Cents

Entered as Second-Class Matter March 27, 1937, at the Post Office at Philadelphia, Pa.
Under Act of March 3, 1879

Controls Useless Nagging Cough

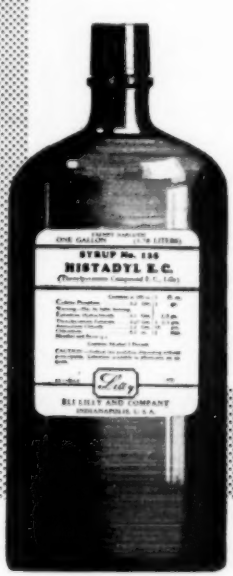
More physicians are prescribing Syrup 'Histadyl E.C.,'° an effective combination of:

- ***. . . Codeine Phosphate a bronchial sedative***
- ***. . . Ephedrine Hydrochloride a bronchodilator***
- ***. . . Thenylpyramine Fumarate an antiallergic***
- ***. . . and Ammonium Chloride an expectorant***

in a pleasantly flavored syrup acceptable to both children and adults. Be ready for the peak demand in the weeks ahead. Order today.

°FEDERAL RECORD OF SALE REQUIRED.

Eli Lilly and Company
Indianapolis 6, Indiana, U.S.A.



Lilly

SYRUP

Available in handy one-pint or economical one-gallon bottles. Order from your favorite Lilly distributor.

'Histadyl E.C.'

(THENYLPYRAMINE COMPOUND E.C., LILLY)

the most popular antiseptic in powder form!

Be sure to maintain adequate stocks of B·F·I, the fast-moving antiseptic first-aid dressing and surgical dusting powder. In addition to its marked bactericidal properties, B·F·I Powder is an excellent astringent, promoting gentle contraction of the skin to arrest oozing secretions.

B·F·I Powder is easy to apply. Sprinkled on cuts, burns, abrasions, chafed skin, scratches, prickly heat and minor wounds, it provides an ideal protective covering — protection against infection, and protection against further irritation.

B·F·I Powder is also valuable as treatment for certain fungus infections of the skin, including "athlete's foot". Sprinkler-top packages: ¼-oz., 1¼-oz. and ½-lb.
Sharp & Dohme, Philadelphia 1, Pa.

B·F·I

ANTISEPTIC FIRST-AID DRESSING AND SURGICAL POWDER

AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

LINWOOD F. TICE, Ph. G., B. Sc., M. Sc., Editor
Kenneth Avis, M. Sc., Editorial Assistant
Charles E. Welch, Jr., B. S., M. A., Editorial Assistant
John E. Kramer, B. Sc., Business Manager

COMMITTEE ON PUBLICATION

E. Fullerton Cook, P. D., Ph. M., M. S., Chairman
Mitchell Bernstein, P. D., M. D., F. A. C. P.
Marin S. Dunn, A. M., Ph. D.
Louis Gershenfeld, P. D., Ph. M., D. Sc.
J. W. Sturmer, Phar. D., Ph. M., D. Sc., Secretary
Ivor Griffith, P. D., Ph. M., D. Sc., F. R. S. A., ex officio

Vol. 124 DECEMBER 1952 No. 12

CONTENTS

Editorial:

Where Lies Peace? 396

Articles:

Benzyl Alcohol in Parenteral Solutions. By Louis Gershenfeld 399

Anti-Tuberculous Drugs—A Review 404

Comparative Study of the Disintegration Time Determination of Compressed Tablets According to the U. S. P. XIV and a Modified British Pharmacopoeia (1948) Method. By Wayne M. Grim and William E. Gordon, Jr. 410

Selected Abstracts 414

Index to Volume 124 421

EDITORIAL

WHERE LIES PEACE?

AS the year 1952 draws to its close most Americans look to 1953 with the sincere hope that some way out of the world's current dilemma may be found. The overwhelming victory of General Eisenhower at the polls in November is evidence of the desire for some change that will bring an end to the war, hatred and bitterness which pervades the earth.

The recent Democratic administration was accused by some extremists of all sorts of derelictions, some even bordering on treason. We doubt very much whether there were any of the top leaders who failed to do the best they knew under the trying circumstances with which they were constantly faced. In the words of one "there seems to be some new emergency every day."

The real hope which is offered by our new leaders is that they will bring fresh thinking and a new approach to those vast and intricate problems which face us. There is every evidence that General Eisenhower is laying the groundwork for an efficient and smoothly functioning government. His selection of an official family has been judicious and without dictation from professional politicians. It seems that we can expect progress.

Americans must, however, face certain realities and problems if they are to avoid disillusionment and even national calamity. The mere fact that we have a new administration headed by a man of such stature as Eisenhower is no guarantee of an immediate or even an early end to our problems. In spite of his very best efforts our path is likely to be difficult and perhaps painful. Contrary to the thinking of many, our present problems are not solely the result of bad decisions in Washington over the past two decades. At most these could only aggravate the situation, not cause it.

The underlying sources of world unrest can be traced to man's failure to make social and political progress at somewhere near the same speed at which he has made technical progress. Civilization, today, is like a group of undisciplined youngsters playing policemen

and robbers with loaded pistols instead of toy guns. There are still too many who feel that the only approach in solving our differences is to make frightening noises to scare our enemies and then if this fails kill them. This technique is older than man himself and it does not speak well for his claim of civilization.

We can arm as can our enemies—and both are engaged in this pursuit. We can attempt to destroy Russia and we might succeed but no mature and thinking person can believe that even this would bring us peace. This process carried to its bitter end would find only two people left in the world, these locked in mortal combat and each saying through clenched teeth "we shall have peace when this task is over." Peace, indeed, one of them would have until at last the utter loneliness and despair in a world without fellowmen dawned on his conscious mind. Then in desperation he would take his own life and the noble experiment of civilized man would end forever.

The real sources of man's present dilemma lie all about us but we are so smug, so bigoted and so unwilling to face reality that we prefer to blame some evil men who are far away rather than ourselves.

Man's lot shall be war and suffering until he is willing to face certain inescapable truths. While we profess to love our fellowman actually we do not. While we claim no racial prejudice, our new McCarran Act admits only 100 Chinese a year, and negroes still may not dine in many Washington restaurants. While we profess to love our "brothers" overseas we refuse to give them even our surpluses, preferring to destroy them. We profess certain religious beliefs and then violate every rule of conduct, including the Golden Rule. Still, however, many are those who attend church regularly with smug satisfaction and not the slightest twinge of conscience.

As a case in point—our penicillin manufacturers are presently engaged in a price war because production exceeds demand. Penicillin has been sold recently for as little as 2 or 3 cents a hundred thousand units. Yet at this very moment a tearful mother somewhere in the world is watching her baby die when 1 vial of penicillin would save its life. Does this tragedy really concern us? Do we share in this mother's grief?

We can build our armies and bigger and better atomic bombs and we can haggle and wrangle in the United Nations. All of this

is meaningless. When each of us is truly concerned over the hunger, the illness, the suffering, the hopes and aspirations of the meanest and lowest person in the world be he Chinese, Arab, or African we shall have peace. Until that time peace shall be only a lull between wars, with each lull more brief and each war more horrible.

In our national efforts to bring about world peace every citizen has a responsibility. The world looks to America for leadership and it will take vision, understanding and sacrifice if we are to succeed. Military preparedness will not and can not replace the positive steps toward the brotherhood of man, which alone will bring an enduring peace.

L. F. Tice

BENZYL ALCOHOL IN PARENTERAL SOLUTIONS *

By Louis Gershenfeld **

SINCE the discovery of its anesthetic action, benzyl alcohol has been employed as an efficient local anesthetic (1). In concentrations up to 5%, benzyl alcohol has been used in parenteral solutions serving a two-fold purpose: as an anesthetic and as a bacteriostatic agent (2). A number of marketable solutions or suspensions for intramuscular or subcutaneous injection contain 1 to 3% of benzyl alcohol to minimize pain which may result from an injection.

Subcutaneous or intramuscular injections of benzyl alcohol (undiluted) produce irritation and necrosis in tissue, although the slough produced is sterile in nature (3). Post-operative histories of patients on whom benzyl alcohol had been used as a local anesthetic showed a rapid healing with no infection. The concentrations ranged from 0.5% to 4%; tissue irritation was not detectable (3).

The fact that a pyogenic effect was not produced when benzyl alcohol was injected subcutaneously or intramuscularly seemed in some measure at least to indicate benzyl alcohol might possess antibacterial activity. Aqueous solutions of benzyl alcohol were reported to possess antibacterial activity against a number of bacteria. "Experimentation with 0.5% benzyl alcohol showed that Friedlander's bacillus was killed in nineteen hours and pyocyaneus bacilli were destroyed in 24 hours. With a 1% solution of benzyl alcohol there was evidence of a more marked and rapid bactericidal action" (2). The germicidal activity of benzyl alcohol in varying concentrations against the gonococcus as the test organism revealed that 3% and 2% solutions of benzyl alcohol "possessed 'absolute' killing power in five minutes" (4). The purpose of this study was to determine the antibacterial efficiency of benzyl alcohol, in concentrations commonly used, against different bacteria and bacterial spores.

---

* Presented to the Scientific Section, A. Ph. A., Centennial Meeting, Philadelphia, August, 1952.

** Director, Department of Bacteriology, Philadelphia College of Pharmacy and Science.

Experimental

The technique used in testing the bacteriostatic action of benzyl alcohol was a modified Kolmer method using nutrient broth (5).

The test organisms used in testing the bacteriostatic action of benzyl alcohol was a modified Kolmer method using nutrient broth (5).

The test organisms used were: *Staphylococcus aureus* (No. 209), *Escherichia coli communis, Bacillus subtilis* (vegetative form), *Bacillus megatherium* (vegetative form), and *Bacillus mesentericus* (vegetative form). Each of these organisms was obtained from an agar stock culture, transferred thereafter for five days on nutrient broth before being used. The last 24-hour old broth culture of each organism was employed in the test. The organisms in each 24-hour old culture were diluted with sterile broth to give dilutions of: 1:10, 1:100, and 1:1000.

The test spores used were: *Bacillus subtilis, Bacillus mesentericus* and *Bacillus megatherium.* The spores were obtained from 16 month old cultures grown on agar slants of F.D.A. medium. These suspensions were centrifuged, washed twice and were resuspended in sterile isotonic saline solution. They were then diluted separately in sterile isotonic solution of sodium chloride to give respectively: 10,000, 100,000 and 1,000,000 spores per ml. These stock suspensions were stored in the refrigerator.

The solubility of benzyl alcohol in water at 17°C. is approximately 4% (1:25). A 3.5% dilution was found to give a completely clear solution of the benzyl alcohol in the nutrient broth. Dilutions of 1:33 to 1:1,000 were used in this study.

Two identical sets of tubes containing broth were prepared. The final pH of the medium in one set was adjusted to approximately 7.1. The tubes in the other set were not adjusted and the original pH was 6.5. Benzyl alcohol has a pH of 7.0 and so did not substantially alter the final pH of the medium.

One tenth ml. of each suspension of the respective test organism and of the dilution of each spore suspension was added separately to 9.9 ml. of each of the respective dilutions of benzyl alcohol in nutrient broth (ranging from 1:33 to 1:1,000). Positive controls in nutrient broth (which did not contain benzyl alcohol) were run, using each bacterial dilution and each spore suspension to verify viability. A

tube of nutrient broth (which contained neither organisms nor benzyl alcohol) was used as a control to make certain that the medium was not contaminated.

Identical sets were prepared for two different storage (or incubation) temperatures for all dilutions of the benzyl alcohol—spore and bacteria mixtures. These temperatures were: 24°C. (room temperature) and 37°C.

The presence or absence of growth in all tubes at the different storage temperatures was noted daily for seven days. All tubes revealing no growth were then incubated at 37°C. for another 7 days. At the end of a total of fourteen days incubation, tubes revealing no growth were subcultured by transplanting one-half of the contents of each tube to flasks containing 150 ml. of sterile nutrient broth, and these were incubated for one month at 37°C. When a tube remained clear during the initial fourteen day incubation period and then upon subculturing showed growth, bacteriostasis was indicated. On the other hand, if no growth appeared in subcultures of the clear tube, it was assumed that particular dilution of benzyl alcohol was effective

Findings

At the end of fourteen days' incubation, dilutions of 1:250 and weaker concentrations of benzyl alcohol containing 0.1 ml. of the 1:1000 dilution of *Staphylococcus aureus* (209) showed growth, while dilutions of 1:200 and stronger concentrations of benzyl alcohol containing 0.1 ml. of 1:1000 dilution of benzyl alcohol showed no growth. Subsequent subculturing of the latter tubes in nutrient broth showed no growth. The same organism in 0.1 ml. of a 1:100 dilution of an inoculum showed growth in dilutions of 1:250 and weaker concentrations of benzyl alcohol at the end of fourteen days, while 0.1 ml. of a 1:100 dilution of the bacterial culture in a 1:200 and stronger concentrations of benzyl alcohol showed no growth. However, upon subculturing at the end of fourteen days, the 1:200 and a 1:175 dilutions of benzyl alcohol showed growth. With 0.1 ml. of a 1:10 dilution of inoculum of *Staphylococcus aureus* (209), the fourteen days' incubation exhibited growth at concentrations of 1:200 and weaker and no growth at 1:175 and in stronger concentrations. The subculture of all tubes showing no growth revealed growth at the end of 24 hours, indicating that these concentrations were only bacteriostatic.

Using *Escherichia coli communis* as the test organism, 0.1 ml. of a 1:1000, 1:100, and 1:10 dilutions of the latter were inoculated separately into tubes of benzyl alcohol, (1:250 and weaker). At the end of fourteen days, growth was displayed in all of the tubes. At the end of this same time, 0.1 ml. of the respective dilutions of the same organism gave no growth in 1:200 dilutions and stronger concentrations of benzyl alcohol. Subcultures of all the 1:200 and stronger dilutions of benzyl alcohol revealed no growth.

When 0.1 ml. of a 1:1000 dilution of inoculum of *Bacillus subtilis* was transplanted into dilutions of benzyl alcohol, (1:250 and weaker), at the end of fourteen days' incubation, growth occurred, but a 1:200 and stronger dilutions of benzyl alcohol with the same inoculum at the end of fourteen days showed no growth. The tubes, however, upon subculturing for 24 hours revealed growth. One-tenth cc. of a 1:100 dilution of inoculum of the organism gave growth at the end of fourteen days in a 1:200 and weaker dilutions of benzyl alcohol, while the same inoculum in a 1:100 and stronger dilutions of benzyl alcohol gave no growth. Upon subculturing the latter dilutions growth was revealed. Furthermore, 0.1 ml. of a 1:100 dilution of *Bacillus subtilis* in dilutions of benzyl alcohol 1:50 and weaker, (which had displayed no growth at the end of 14 days) revealed growth in all subcultures. When 0.1 ml. of a 1:10 dilution of inoculum of *Bacillus subtilis* in a dilution of benzyl alcohol 1:200 and weaker was incubated for fourteen days, growth appeared; no growth appeared in 1:100 and stronger concentrations of benzyl alcohol with 0.1 ml. of the same inoculum. These dilutions of benzyl alcohol (1:100, 1:50, and 1:33) containing the 1:10 dilution of the test organism gave growth when subcultured for 24 hours.

One-tenth ml. of a 1:1000, 1:100, and 1:10 dilution of *Bacillus megatherium* and *Bacillus mesentericus* all revealed growth in dilutions of benzyl alcohol (1:200 and weaker) at the end of the fourteen days' incubation; while with 0.1 ml. of the respective dilutions of both of the test organisms, dilutions of benzyl alcohol (1:100 and stronger) displayed no growth at the end of fourteen days, nor was growth obtained after subculturing these tubes.

When using sixteen month old cultures of *Bacillus subtilis*, *Bacillus mesentericus* and *Bacillus megatherium* (spores in each instance), benzyl alcohol in concentrations of 1% or stronger was found to be bacteriostatic against the three different dilutions of all of the spore suspensions.

Summary

Benzyl alcohol in concentrations varying from 1:1000 to 1:33 was tested for its antibacterial efficiency against five different test bacteria and three different spore suspensions. The technique used was a modified Kolmer technique for bacteriostasis using nutrient broth. The test organisms were 24 hour old broth cultures of *Staphylococcus aureus* (209), *Escherichia coli communis*, *Bacillus subtilis* (vegetative), *Bacillus mesentericus*, (vegetative) and *Bacillus megatherium* and sixteen month-old cultures of the last three mentioned bacteria (all spores).

Benzyl alcohol in concentrations of one percent or stronger was found to be bacteriostatic against the test bacteria and bacterial spores used in this investigation.

Acknowledgment

These studies were conducted over the past few years employing different strains of the test organisms. Different workers aided as technical assistants. Appreciation for this is extended to David S. Ziv and Oscar A. Brown.

REFERENCES

(1) Gruber, C. M., "Discovery of New Anesthetics", Boston and Medical Surgery Journal, *180*, 288, 1949.

(2) Macht and Nelson, "Antispetic Action of Benzyl Alcohol", *Proceedings for the Society Exp. Biology and Medicine*, *16*, 25, 1918-1919.

(3) Gruber, C. M., "The Pharmacology of Benzyl Alcohol and its Esters", Journal of Laboratory and Clinical Medicine, *9*, 15-33, 1923-1924.

(4) Macht, D., Satani, Y., and Swartz, E. O., "A Study of the Antiseptic Action of Certain Local Anesthetics". *Journal of Urology*, *4*, 355-61 (1920).

(5) Kolmer, J. A. et al., *Approved Laboratory Technique*, 5th ed., New York, Appleton-Century-Crofts, 1941.

ANTI-TUBERCULOUS DRUGS

A Review

THE announcement early in 1952 that the substance, isonicotinyl hydrazide (isoniazid), had marked tuberculostatic properties caused great excitement. No therapeutic regimen for tuberculosis had ever proven entirely satisfactory, and it was thought by many that possibly here might be the wonder drug that would bring tuberculosis under complete control.

A tremendous amount of clinical research has been done on isoniazid and its comparison with other tuberculostatic drugs during the past year. While it is too soon to give the final answer, much has been learned and the relative merits and demerits of the various drugs used in tuberculosis rapidly are becoming clear.

Tuberculosis is a much more prevalent disease than many persons realize. It has plagued mankind since before recorded history. About 15 million persons in the world suffer with the disease. The mortality rate varies from a reported 260 per 100,000 inhabitants in Portugal (1950) to a low of 7 per 100,000 in Denmark. The deaths caused by tuberculosis in India (no data) are undoubtedly several hundred thousand per year and it is estimated that between 2 and 5 million deaths are caused by it each year throughout the world.

It is considered quite certain that many more people suffer with a subclinical case of tuberculosis than are diagnosed as tuberculous and treated. Some workers claim that as high as 90 per cent of the general population has been infected by tuberculosis to some extent before adulthood. In most of these, the disease is undetected and no medical treatment is given.

Prior to the development of tuberculostatic drugs, the treatment of tuberculosis was based exclusively on complete rest, a good diet, fresh air, and—in some cases—pneumothorax or thoracoplasty.

For many years, a search was made for a drug which might prove useful in tuberculosis. Among those which gave promise were the sulfones. Experience with these showed them to be satisfactory for leprosy but not tuberculosis. The discovery of streptomycin by Waksman and the announcement that it had marked tuberculostatic

action changed the entire approach to the treatment of tuberculosis. At first, it was hoped that chemotherapy with streptomycin might prove completely effective in curing tuberculosis, but this hope has not been realized. Streptomycin still remains our best drug for the treatment of selected cases but, today, we know its limitations and how it can be used to best advantage to avoid its shortcomings as much as possible.

Other tuberculostatic drugs have been studied extensively in the last few years. Among the more important are the thiosemicarbazones (including amithiozone), para-aminosalicylic acid, and isonicotinyl hydrazide (isoniazid). Some recent reports have been published which give us a fairly reliable picture of the current status of these several drugs and their relative merit.

Chemotherapy should not be the only approach considered by the physician in the treatment of tuberculosis. The duration of the disease, the extent of the disease, previous treatment with drugs, the roentgenographic findings—all are important factors. In some cases, chemotherapy combined only with bed rest may provide adequate treatment. In others, chemotherapy should only be an adjunct to more drastic measures such as collapse therapy or resection.

Chemotherapy, in any event, is a long term process and no drug or combination of drugs known will produce rapid cures. While the patient may show rapid subjective improvement, this is not a sign of cure. With all tuberculostatic drugs, the two problems, drug resistance and toxicity, are the sources of difficulty. Combined therapy using more than one drug and given at a dosage level which minimizes toxicity is the preferred approach.

In the early days of chemotherapy in tuberculosis, the frequency of toxic reactions and the emergence of drug resistant strains led most authorities to recommend the use of such drugs as streptomycin only when other treatment was unsatisfactory. Today, antimicrobial therapy is used much more frequently and is, in fact, recommended in all cases where there is a liklihood of reversing the disease. It is, of course, imperative that chemotherapy be used at once in such serious conditions as miliary tuberculosis or tuberculous meningitis. It is also quite important that chemotherapy be used to prevent postoperative complications in tuberculosis. In this connection, it is unfortunate if surgery must be performed at such a time that the patient harbors drug resistant organisms. For this reason, the physi-

cian must carefully study each patient and judge the desirability of chemotherapy as well as its proper timing.

Streptomycin and Dihydrostreptomycin

These drugs are still the most effective tuberculostatic agents available. It is now believed that they are of about equal potency. In the early days of streptomycin therapy, large doses were given and many toxic reactions were reported. In acute infections caused by organisms other than *M. tuberculosis*, large doses for a short period are relatively safe. In tuberculosis, however, therapy is required for very long periods and such large doses cannot be given without toxic effects. It has also been found that it is not necessary nor even desirable to give streptomycin daily. The administration of 1 Gm. intramuscularly 2 or 3 times weekly or 2 Gm. every 3 days is as effective as the use of daily doses of 1 Gm. Such intermittent therapy produces fewer toxic reactions and few resistant strains.

Streptomycin and dihydrostreptomycin are excreated by the kidney. If kidney function is impaired, the drug may cumulate and give rise to toxic effects. It is wise to determine kidney function in doubtful cases before treatment. If kidney function is below normal, the dose should be adjusted downward to allow for this.

Allergic reactions including drug fever, dermatitis, and neurological reactions are the most common toxic reactions. Streptomycin seems to produce these more frequently than does dihydrostreptomycin. The neurotoxic reactions are vestibular dysfunction and impaired hearing. Reducing the dose or discontinuing the drug may be necessary to prevent a serious neurotoxic reaction. An auditory test (high pitch) and a test for vestibular function should be done at regular intervals (3-4 weeks) during treatment so that a developing toxic reaction may be detected early.

In very serious tuberculous infections, the decision to continue therapy in spite of toxic reactions may be necessary. Streptomycin seems to be more damaging to vestibular function than is dihydrostreptomycin, while the reverse is true with regard to the auditory nerve.

Streptomycin and dihydrostreptomycin are available in ampuls as the sulfate or the hydrochloride. It is also available as the calcium chloride complex.

Para-Aminosalicylic Acid (PAS)

This drug is only weakly tuberculostatic when given alone. Its chief and most important use is in combined therapy with streptomycin. Given with streptomycin, it greatly reduces the emergence of streptomycin resistant strains of *M. tuberculosis*. One study has shown a reduction in the incidence of streptomycin resistant strains from 78 per cent using streptomycin alone to 4 per cent using combined therapy.

Para-aminosalicylic acid should be given daily, preferably as the sodium salt. The daily dose should be 12 Gm. (in divided doses) in terms of PAS. The sodium salt should be given in somewhat higher doses so that this equivalent of PAS is given. The drug is rapidly excreted and, therefore, it must be given in frequent large doses.

Gastric distress is sometimes observed in patients taking PAS or its sodium salt. Enteric tablets have been supplied in an effort to reduce gastric irritation.

The drug probenecid, *p*-(di-*n*-propyl sulfamyl) benzoic acid, retards the excretion of *p*-aminosalicylic acid sufficiently so that, if it is given concurrently, the dose of *p*-aminosalicylic acid can be reduced to 8 Gm. per day.

Sodium *p*-aminosalicylate has also been given parenterally as a means of avoiding gastrointestinal distress.

Both *p*-aminosalicylic acid and its sodium salt are available as powder and tablets.

Isonicotinyl Hydrazide

This drug, also known as isoniazid and under a host of proprietary names, was reported early in 1952 as a potent tuberculostatic drug. The drug is relatively non-toxic and can be given both orally and parenterally. The dose is 150-300 mg. daily taken in divided doses. Patients on isoniazid show rapid improvement with weight gain, reduction of bacteria in sputum, and lowering of blood sedimentation rate.

Early hopes that this drug alone would provide adequate chemotherapy in tuberculosis have not been realized. Clinical studies have shown it to be very valuable when used alone, but the emergence of strains resistant to it has been established.

In a clinical evaluation of isoniazid as compared with combined streptomycin *p*-aminosalicylic acid therapy, the results after 3 months were quite analogous. Isoniazid did give slightly better results; particularly, insofar as weight gain was concerned. A comparison of the emergence of resistant forms, however, gave the following results. After one month, of 104 cases tested, 78 per cent were sensitive; 12 per cent, doubtful; and 11 per cent, resistant. After 2 months, of 58 available specimens, 29 per cent were sensitive; 19 per cent, doubtful; and 52 per cent, resistant. After 3 months, of 21 available specimens, 3 were doubtful and 15 (71 per cent) were resistant. These figures are far above those which are known to prevail using combined streptomycin-PAS therapy. They point to the inadvisability of using isoniazid alone in treating tuberculosis.

Preliminary studies using streptomycin, 1 Gm. 3 times weekly, plus isoniazid 150-300 mg. per day are most encouraging. It appears that this combination is the equal of and possibly better than streptomycin-PAS. It has the further advantage of not being as likely to cause gastric distress and causing more subjective improvement.

The combination of isoniazid and streptomycin may prove the ideal therapeutic approach. It is also possible that streptomycin, isoniazid, and PAS will be found even more useful.

Iproniazid (1-isonicotinyl-2-isopropyl hydrazine), a drug closely related to isoniazid, has very similar tuberculostatic properties. At present, isoniazid seems to be preferred to the isopropyl derivative.

Thiosemicarbazones

The best known representative of this group is amithiozone, also known as conteben, tibione, and myvisone. This drug originated in Germany where it was extensively used. Experience with this drug has shown that it lies somewhere between streptomycin and PAS in its tuberculostatic activity. It is quite toxic, however, causing anemia, liver and kidney damage, and gastrointestinal disturbances. When used in combination with streptomycin, it does not give results comparable to streptomycin-PAS since it does not reduce the emergence of streptomycin resistant forms.

Terramycin

This drug appears to have definite value; particularly, as a substitute for PAS in combined streptomycin therapy. Some patients

cannot tolerate PAS and, in these it may be replaced by a daily oral dose of 5 Gm. of terramycin (plus streptomycin—1 Gm. three times weekly or 2 Gm. every 3 days). Such a regimen seems to compare favorably with streptomycin-PAS therapy. Some gastrointestinal distress may accompany the administration of 5 Gm. of terramycin daily. Clinical studies in which this is reduced to 2 Gm. daily are now under way.

Viomycin

Preliminary studies combining this antiobotic with either PAS or streptomycin have shown that viomycin has some merit. Viomycin has some toxic properties (pain at injection site, allergic reactions, renal irritation) and these would seem to limit its use except in patients who cannot tolerate other drugs.

In conclusion, one should discourage the thought that the eradication of all tubercular infections by chemotherapy is an immediate prospect. The tubercle bacillus has survived for many years and it is highly adaptive. We do have drugs today which are of tremendous value as one of the adjuncts in tuberculosis control. Among these, streptomycin plus PAS is the best established regimen. Streptomycin plus isoniazid may prove superior if early results are corroborated and long term use gives results which are equally good.

It seems reasonable to expect still further progress as new synthetics are evolved based on our current knowledge of chemotherapy and its application in tuberculosis.

COMPARATIVE STUDY OF THE DISINTEGRATION TIME DETERMINATION OF COMPRESSED TABLETS ACCORDING TO THE U. S. P. XIV AND A MODIFIED BRITISH PHARMACOPOEIA (1948) METHOD

By Wayne M. Grim and William E. Gordon, Jr. *

THE British Pharmacopoeia 1948 (1) and the Pharmacopoeia Helvetica (Swiss) Editio V (2) are the two European Pharmacopoeias which have included an official method for the determination of the disintegration time of compressed tablets. The U. S. P. XIV (3) was the first revision to have an official method for the determination of the disintegration time of compressed tablets.

One of the main obstacles in determining the disintegration time is the interpretation of the word, disintegration. It is usually used indiscriminately, so that there is in practice no distinction between solubility time and disintegration time. A compressed tablet put in water will disintegrate or fall apart or it will dissolve slowly. Disintegration as used here means falling apart into smaller particles.

Sperandio *et al.* (4) suggested the following definition for the disintegration time of a tablet: "the time required for a tablet to break up into granules, which are the size of the original granules from which it was compressed". It would seem more practical, however, to change the term "original granules" to "particles small enough to pass through a definite mesh screen". The U. S. P. XIV uses a 10 mesh number 23 (0.025 inch) gauge woven stainless steel wire cloth in its test.

The description of the disintegration time determination for compressed tablets in the Swiss Pharmacopoeia Edition V is not clearly defined. A conical flask is employed and the operator is directed to rotate it from time to time. There are many uncontrolled factors in this test, such as the vigor used in rotating the flask and the time interval between each rotation.

The British Pharmacopoeia (1948) in its test for the disintegration of tablets gives the following procedure: Sufficient water, heated to 37° C., is added to a test tube (15.24 cm. × 2.54 cm.) so that when the stopper is put in place, there is 1.27 cm. of air space remaining. The tablet is added and the tube closed and placed in a water bath maintained at 37° C. The tube is repeatedly inverted at such a speed

* Department of Pharmacy, Philadelphia College of Pharmacy and Science.

that the tablet travels through the water without striking the end of the tube.

A more practical, cheaper, and easier method is described by Steiger and Kiihni (5). This method is not complicated and results obtained with it are very satisfactory and reproducible. This test, in fact, is a modification of that in the British Pharmacopoeia (1948). It is as follows: A tablet is placed in a stoppered test tube (16 cm. $\times$ 2.5 cm.) and containing 50 cc. of distilled water at 37° C. The test tube is inverted as soon as the tablet reaches the bottom stopper. This is continued until the tablet has disintegrated and a time reading has been taken. The main objection to this test is that, like the British Pharmacopoeia (1948) Method, it does not control the size of the disintegrating particles. However, it is worthwhile to compare the result obtained with this test with that of the U. S. P. XIV, on a statistical basis.

A standard used here is the mean square deviation which is the measure of the variability customarily employed in research. The mean square deviation is defined as the square root of the mean of the squared deviations taken from the arithmetical mean of the distribution. The following formula is applicable:

$$\sigma = \sqrt{\frac{\Sigma\ (X - \bar{X})^2}{N}}$$

σ = mean square deviation
X = individual values of disintegration times
$\bar{X}$ = average of disintegration times
N = number of tests
Σ = sum of

This is the direct or long method of calculating the mean square deviation. A shorter and more convenient method of calculation is as follows:

$$\sigma = \sqrt{\frac{\Sigma\ (X - D)^2}{N} - \left[\frac{\Sigma\ (X - D)}{N}\right]^2}$$

σ = mean square deviation
X = individual values of disintegration times
D = lowest value of X or the shortest disintegration time.
N = number of tests
Σ = sum of

COMPARATIVE STUDY OF THE DISINTEGRATION TIME DETERMINATION OF COMPRESSED TABLETS ACCORDING TO THE U. S. P. XIV AND A MODIFIED BRITISH PHARMACOPOEIA (1948) METHOD

By Wayne M. Grim and William E. Gordon, Jr. *

THE British Pharmacopoeia 1948 (1) and the Pharmacopoeia Helvetica (Swiss) Editio V (2) are the two European Pharmacopoeias which have included an official method for the determination of the disintegration time of compressed tablets. The U. S. P. XIV (3) was the first revision to have an official method for the determination of the disintegration time of compressed tablets.

One of the main obstacles in determining the disintegration time is the interpretation of the word, disintegration. It is usually used indiscriminately, so that there is in practice no distinction between solubility time and disintegration time. A compressed tablet put in water will disintegrate or fall apart or it will dissolve slowly. Disintegration as used here means falling apart into smaller particles.

Sperandio *et al.* (4) suggested the following definition for the disintegration time of a tablet: "the time required for a tablet to break up into granules, which are the size of the original granules from which it was compressed". It would seem more practical, however, to change the term "original granules" to "particles small enough to pass through a definite mesh screen". The U. S. P. XIV uses a 10 mesh number 23 (0.025 inch) gauge woven stainless steel wire cloth in its test.

The description of the disintegration time determination for compressed tablets in the Swiss Pharmacopoeia Edition V is not clearly defined. A conical flask is employed and the operator is directed to rotate it from time to time. There are many uncontrolled factors in this test, such as the vigor used in rotating the flask and the time interval between each rotation.

The British Pharmacopoeia (1948) in its test for the disintegration of tablets gives the following procedure: Sufficient water, heated to 37° C., is added to a test tube (15.24 cm. × 2.54 cm.) so that when the stopper is put in place, there is 1.27 cm. of air space remaining. The tablet is added and the tube closed and placed in a water bath maintained at 37° C. The tube is repeatedly inverted at such a speed

* Department of Pharmacy, Philadelphia College of Pharmacy and Science.

that the tablet travels through the water without striking the end of the tube.

A more practical, cheaper, and easier method is described by Steiger and Kiihni (5). This method is not complicated and results obtained with it are very satisfactory and reproducible. This test, in fact, is a modification of that in the British Pharmacopoeia (1948). It is as follows: A tablet is placed in a stoppered test tube (16 cm. $\times$ 2.5 cm.) and containing 50 cc. of distilled water at 37° C. The test tube is inverted as soon as the tablet reaches the bottom stopper. This is continued until the tablet has disintegrated and a time reading has been taken. The main objection to this test is that, like the British Pharmacopoeia (1948) Method, it does not control the size of the disintegrating particles. However, it is worthwhile to compare the result obtained with this test with that of the U. S. P. XIV on a statistical basis.

A standard used here is the mean square deviation which is the measure of the variability customarily employed in research. The mean square deviation is defined as the square root of the mean of the squared deviations taken from the arithmetical mean of the distribution. The following formula is applicable:

$$\sigma = \sqrt{\frac{\Sigma\ (X - \overline{X})^2}{N}}$$

σ = mean square deviation
X = individual values of disintegration times
$\overline{X}$ = average of disintegration times
N = number of tests
Σ = sum of

This is the direct or long method of calculating the mean square deviation. A shorter and more convenient method of calculation is as follows:

$$\sigma = \sqrt{\frac{\Sigma\ (X - D)^2}{N} - \left[\frac{\Sigma\ (X - D)}{N}\right]^2}$$

σ = mean square deviation
X = individual values of disintegration times
D = lowest value of X or the shortest disintegration time.
N = number of tests
Σ = sum of

As was stated before, the mean square deviation is a measure of the variability or deviation of the method. The smaller the value of σ the smaller the deviation.

Four different kinds of tablets were taken for the tests. Ten of each kind were tested by the U. S. P. XIV Method and by the Modified British Pharmacopoeia (1948) Method. A slide rule was used for all calculations.

TABLET A—U. S. P. XIV METHOD

Number of tests	X	X — D	(X — D)²
I	265 seconds	0	0
II	308 "	43	1849
III	325 "	60	3600
IV	335 "	70	4900
V	350 "	85	7225
VI	295 "	30	900
VII	320 "	55	3025
VIII	335 "	70	4900
IX	340 "	75	5625
X	345 "	80	6400
		$\Sigma = 568$	$\Sigma = 38424$

$$\sigma = \sqrt{\frac{\Sigma (X - D)^2}{N} - \left| \frac{\Sigma (X - D)}{N} \right|^2}$$

$$\sigma = \sqrt{\frac{38424}{10} - \left| \frac{568}{10} \right|^2}$$

$$\sigma = \sqrt{3842.4 - [56.8]^2}$$

$$\sigma = \sqrt{3842.4 - 3226.24}$$

$$\sigma = \sqrt{616.16}$$

$$\sigma = 24.8$$

TABLET A—MODIFIED BRITISH PHARMACOPOEIA (1948) METHOD

Number of Tests	X	X — D	(X — D)²
I	305 seconds	0	0
II	343 "	38	1444
III	313 "	8	64
IV	344 "	39	1521
V	315 "	10	100
VI	328 "	23	529
VII	335 "	30	900
VIII	340 "	35	1225
IX	337 "	32	1024
X	329 "	24	576
		$\Sigma = 239$	$\Sigma = 7383$

$$\sigma = \sqrt{\frac{\Sigma\ (X - D)^2}{N} - \left[\frac{\Sigma\ (X - D)}{N}\right]^2}$$

$$\sigma = \sqrt{\frac{7383}{10} - \left[\frac{239}{10}\right]^2}$$

$$\sigma = \sqrt{738.3 - [23.9]^2}$$

$$\sigma = \sqrt{738.3 - 571.2}$$

$$\sigma = \sqrt{167.1}$$

$$\sigma = 12.92$$

Tablet	Method	σ
B	U. S. P. XIV	38.59
B	Modified B. P. (1948)	12.37
C	U. S. P. XIV	9.36
C	Modified B. P. (1948)	4.91
D	U. S. P. XIV	486
D	Modified B. P. (1948)	108.8

Results from these tests show that on a statistical basis the Modified British Pharmacopoeia (1948) Method is more accurate than the U. S. P. XIV Method, because on every tablet used the mean square deviation was smaller by the Modified B. P. (1948) Method proving the deviation is smaller. Although this is true, the Modified B. P. (1948) Method will probably never be used widely because of the extensive amount of manual labor involved in carrying out the test and because of the inability to control accurately the size of disintegrated particles. In these respects the U. S. P. XIV Method is more convenient and more accurate.

REFERENCES

(1) British Pharmacopoeia 1948.

(2) Pharmacopoeia Helvetica Edito V.

(3) United States Pharmacopoeia, Fourteenth Revision.

(4) G. J. Sperandio et al. *J. Am. Pharm. Assn. (Sci. Ed.), 37,* 71 (1948).

(5) K. Steiger and E. Kiihni, *Pharmac. Acta. Helv. 26,* 313 (1951).

SELECTED ABSTRACTS

The Prolongation of the Action of Hypotensive Drugs. Smirk, F. H. *The Lancet 263*:695 (1952). If the hypotensive effect of drugs used for that effect could be prolonged there would be a lessening in the fluctuation of the blood pressure and of the load on the circulatory system. More relief could be obtained for patients whose headaches are not sufficiently relieved by the short-acting effect of oral or aqueous injections of hypotensive drugs.

The author reported the effect of polyvinylpyrrolidone (p.v.p.), dextran and vasoconstrictors on hexamethonium bromide (H. M. B.) and hexamethylene bis-ethyldimethylammonium bromide (M & B 1863). It was found that a 25 per cent solution of p.v.p. (M. W. 75,000) or a 20 per cent solution of dextran (M. W. 20,000) prolonged the effect of either of the hypotensive agents by subcutaneous injection for as long as 5 to 8 hours. Further prolongation may be obtained by the addition of 1:200,000 to 1:100,000 adrenaline hydrochloride or mucate or of 1:2000 ephedrine hydrochloride. However, it is necessary to increase the dose of H. M. B. by at least 30 per cent when incorporated into a slow absorption vehicle, in order to maintain effective therapy.

It was also found that the use of oral supplements of H. M. B., given after an injection when the blood pressure began to rise, produced as good control as three subcutaneous injections of the aqueous solution. However, this control was not as good as obtained with subcutaneous injections of the substance in a slow absorption vehicle at intervals of every 6 hours, for three doses.

The author pointed out that the dose employed had to be developed for each individual.

No toxic effects were evident. Although there are some objections to the use of p.v.p. it was felt by the author that the small amount given in this therapy was safe. Dextran of larger molecular weight (75,000) did produce lumps and local irritation at the sight of injection but the dextran of 20,000 M. W. seemed to be satisfactory.

Ascorbic Acid Content of Preserved Lemon Juice. Timmington, H. *Pharm. J. 169*:118 (1952). The British Pharmaceutical Codex 1949 contains a statement that "lemon juice contains about 25 mg. to 95 mg. of ascorbic acid per 100 ml. in the fresh juice and about 15 to 40 mg. per 100 ml. in the preserved juice . . .". The author disputed the validity of the ascorbic acid content of preserved lemon juice. It was stated that many samples of juice preserved with sulfur dioxide had been examined and had rarely been found to contain more than 5 mg. of ascorbic acid per 100 cc.

A study was made of the rate of fall of ascorbic acid content in preserved juices under various storage conditions, in the refrigerator, in the dark at room temperature, and on an open shelf at room temperature. The rate of destruction of synthetic ascorbic acid was also compared with that of the naturally occurring acid. An imported sample of juice containing 424 p.p.m. of sulfur dioxide and assayed as containing 1.2 mg. of ascorbic acid was fortified with 25 mg. of the synthetic vitamin. At the end of 35 days the vitamin content was 3.2 mg., 0.6 mg. and 0.6 mg. for the juice stored in the refrigerator, in the dark, and on the shelf, respectively. A sample of fresh juice was assayed as having 48.8 mg. of ascorbic acid per 100 cc. It was preserved with 250 p.p.m. of sulfur dioxide and half of the sample was fortified with 48.8 mg. of synthetic ascorbic acid. At the end of 74 days the unfortified assayed at 13.8 mg. and the fortified at 62.0 mg. of ascorbic acid, when stored in the refrigerator. However, at the end of 25 days the unfortified assayed at negligible and the fortified at 36.4 mg. of ascorbic acid, when stored on an open shelf.

These findings indicate that the ascorbic acid content of preserved lemon juice falls below that stated in the Codex after about 2 weeks when stored under normal conditions and after about 2 months in the refrigerator. The synthetic vitamin appeared to be slightly more stable in the presence of sulfur dioxide than the natural vitamin.

Sensitivity to Ointments Containing Wool Fat. Schwarzfeld, H. K. *U. S. A. F. Med. J. 3*:1371 (1952). The author stated that although dermatitis from lanolin and aquaphor are encountered the incidence of such sensitivity is very low. He stated that only 3 or 4 cases of lanolin and aquaphor sensitivity were found in about 2500

tests with topical therapeutic agents, representing a total of about 50,000 patch tests with various topical agents.

In a series of 10 selected patients tested by the author 2 were found to be sensitive to both lanolin and aquaphor, 4 to lanolin alone, and 4 to aquaphor alone. Four of these patients, 1 sensitive to lanolin alone, 2 to aquaphor alone, and 1 to both, were given additional tests. None of them were found to be sensitive to cholesterol crystals, 10 per cent cholesterol in mineral oil, nor 35 per cent cholesterol in peanut oil. If cholesterol had been the common denominator causing the sensitivity to lanolin and aquaphor all of the patients should have reacted to the purified cholesterol as well as to both lanolin and aquaphor. Cholesterol had been blamed for the sensitizing effect by some previous authors.

The author suggested that although the sensitivity to ointments containing lanolin is not common at the present time the increased number of consumer products containing lanolin will provide opportunity for more contact by the public, with an increased opportunity for sensitization. He stated that some cases of eczematous contact-type dermatitis can be caused, aggravated, or maintained because of hypersensitivity to lanolin. In some patients rapid improvement follows the removal of the offending substance, but in other cases traces of wool fat in clothing or other hidden sources may retard recovery.

The Treatment of Meningitis Due to Haemophilus Influenzae With Chloramphenicol and Sulfadiazine. Ross, S., Rice, E. C., Burke, F. G., McGovern, J. J., Parrott, R. H., and McGovern, J. P. *New England J. Med. 247*:541 (1952). Fifteen infants and children with meningitis caused by *Haemophilus influenzae* were treated with a combined chloramphenicol and sulfadiazine therapy. Chloramphenicol, in the form of a microcrystalline suspension, was given initially by intramuscular injection in a single daily dose of 100 to 150 mg. per Kg. of body weight. As soon as the condition of the child permitted, the injections were discontinued in favor of 100 to 150 mg. of chloramphenicol palmitate orally, daily, in divided doses. The latter compound was favored because of its greater palatability for children. In addition to the chloramphenicol

an average of 0.3 to 0.4 Gm. of sulfadiazine per Kg. of body weight was given daily. This was reduced to 0.15 to 0.3 Gm. during the convalescent stage. Likewise, the sulfadiazine was given parenterally until the condition of the child permitted oral administration. Therapy was continued for 10 days or longer.

Of this number of patients, 13 recovered and 2 died. The two that died were infants of 2 and 12 months of age who had been ill for 9 and 10 days, respectively, before admission to the hospital. One patient who recovered showed some transitory weakness of the lower extremities.

Whether or not the combined therapy is better than therapy with chloramphenicol alone will require further study. Other investigators had reported as good results from the use of chloramphenicol alone. The authors suggested that severe cases might show better results from the combined therapy.

The authors also stated that the rapidity of recovery in these cases surpassed that produced by any other type of therapy used previously by them. They also recommended that hematologic studies be done frequently during the course of chloramphenicol therapy.

The Development of Bacterial Resistance as a Factor in Antibiotic Synergism and Antagonism. Klein, M. and Schorr, S. E. *Bact. Proceedings,* p. 121 (1952). The antagonistic and inhibitory action of combinations of two of the following antibiotics: penicillin, aureomycin, chloramphenicol, streptomycin, and terramycin, was determined against *Escherichia coli, Staphylococcus aureus, Shigella paradysenteriae,* Group A streptococcus, and a paracolon bacillus. Growth was measured turbidimetrically using a trypticase soy broth medium.

The authors found that either synergism or antagonism could occur with the same combinations of two drugs. This depended to a limited degree upon the concentration of the two drugs and to a significant degree upon the test organisms themselves. The characteristic of the test organism which was most closely associated with synergism or antagonism was the presence or absence of a developed

resistance to each of the antibiotics. Thus synergism was regularly found when the test bacteria showed an increased resistance after 24 to 48 hours growth in the presence of each of the antibiotics and when the combined drugs markedly reduced this increase in resistance. When the combined drugs failed to inhibit the development of resistance no synergism was found to be present even though the bacteria developed a resistance to each of the antibiotics after growth in their presence. Synergism also was not obtained when the test bacteria failed to develop resistance initially when grown in the presence of each of the antiobiotics. In fact, under some conditions of drug concentration antagonism rather than synergism was obtained.

The Effect of Prolonged Administration of Terramycin on Fecal Flora. Spaulding, E. H. Tyson, R. R. and Casey, J. A. *Bact. Proceedings,* p. 113 (1952). Terramycin was administered for as long as 50 days to 19 patients essentially free from gastrointestinal disorders. The antibiotic was given orally in doses of 1.5 or 3 Gm. daily. The authors found that the oral administration of terramycin was not effective as an intestinal antiseptic. The principal effect was to increase the total number of organisms 10 to 100 fold and to cause the retardation of *E. coli* and the multiplication of Proteus organisms and enterococci. If these organisms escape from the bowel they will be more prone to cause infection than the original flora.

The normal fecal flora was rapidly altered by the 3 Gm. schedule. *E. coli* was rapidly replaced as the predominant type by Proteus or enterococci, occasionally by yeasts or Aerobacter. When the drug was stopped *E. coli* reappeared promptly, but organisms predominant during the drug therapy sometimes disappeared and sometimes persisted. A second period of administration of terramycin did not produce a complete or prolonged reduction in *E. coli.* Variability was also found in the susceptibility of the organisms. Some strains were recovered from feces containing 3000 to 6000 micrograms of terramycin per Gm. but were susceptible *in vitro* to 10 micrograms. On the other hand, some relatively resistant forms by *in vitro* tests disappeared more promptly than other more susceptible bacterial types.

Streptomycin in the Treatment of Chronic Tuberculosis. Clarke, Owen. *Brit. Med. J.* No. 4785:644 (1952). The use of streptomycin in the treatment of the chronic, ambulant case of pulmonary tuberculosis has received little attention. In many of these cases the only bar to reasonable activity and employment is a persistent, positive sputum. The author reported a study made to determine the effect of streptomycin and para-aminosalicylic acid (PAS) on producing a negative sputum in such cases.

The treatment at first employed was 1 Gm. of streptomycin intramuscularly daily, usually for 90 days. But, this was later reduced to 1 Gm. twice weekly for 26 doses. The PAS was given daily and concurrently in tablet and cachet form in a dose of 14.1 Gm.

The sputum was converted to negative initially in 23 of the 24 patients in this study. Subsequently, 14 of the patients remained negative up to 2 years. Five patients had isolated positive sputum tests and 4 reverted to positive after a period of negative sputum tests.

Complications might have been expected from (1) toxic symptoms due to streptomycin and PAS; (2) development of a resistant strain of tubercle bacilli; or (3) clinical deterioration. It was found that the symptoms of giddiness, visual or aural disturbances, nausea or diarrhea did not develop. Even the usual abdominal disturbances associated with PAS therapy were found to be much less in the ambulatory patients than in bed patients. Resistant strains of bacteria did not develop for, in no cases in this series did a strain become resistant to 1 unit of streptomycin per cc. No deterioration was found in any of the patients given this therapy. However, the patients were selected with great care. The positive sputum was the only adverse clinical finding in the patients selected.

The author was enthusiastic about the possibility of converting the sputum of chronic, ambulatory, pulmonary tuberculosis patients without interfering with the ordinary day's work, as suggested by the results in these cases.

Development of Sensitivity to PAS and Streptomycin. Jeffery, B. and Borrie, P. *Brit. Med. J.* No. 4785:647 (1952). The case history of a patient is given in whom a severe general toxic reaction developed as a result of combined PAS-streptomycin therapy.

The skin, alimentary tract, liver, kidney, and bone marrow all gave evidence of considerable damage. Later, hypersensitivity to penicillin also developed.

The streptomycin was given in a dose of 1 Gm. daily and the PAS in a daily divided dose of 18 Gm. After 27.5 Gm. of streptomycin and 504 Gm. of PAS had been given the reaction developed.

Treatment of the reaction included discontinuation of therapy. Diphenhydramine hydrochloride was given in a dose of 50 mg. twice a day by mouth and mepyramine hydrogen maleate cream was applied to the skin. Intravenous calcium gluconate and intravenous sodium thiosulfate produced little or no alleviation. Calamine lotion with 1 per cent phenol produced a soothing effect on the rash. Adrenalin given subcutaneously in a 0.5 cc. dose every 6 hours may or may not have aided in the clearing of the rash. The sore mouth was relieved by holding in the mouth for several minutes a 1:6 solution of sodium sulfate. The patient was encouraged to consume glucose and protein drinks.

Patch tests showed a strong reaction to PAS, meta-aminophenol, streptomycin, and dihydrostreptomycin. There was no reaction to sodium salicylate.

The authors discussed to some extent the implications of the development of such sensitivity reactions and their relation to subsequent therapy. They recommended that any patient showing sensitivity to these drugs should be patch tested in order to inform the patient of the drugs which must be avoided. They particularly pointed out the possibility of sensitivity reactions to other drugs with an aminophenol or nitro group in the para position, such as sulfonamides, picric acid, etc., when sensitivity to PAS has developed.

The prompt, prolonged

vasoconstrictive action of

Neo-Synephrine®

The highly effective

antihistaminic action of

Thenfadil®

The potentiating

preservative action of

Zephiran® chloride

NTZ NASAL SOLUTION

TRADEMARK

A Synergistic Combination

Stock this new triple action decongestant
in anticipation of the coming winter season
of colds, rhinitis, and sinusitis, during which
NTZ Nasal Solution will be advertised
and detailed extensively to physicians.
Available in 1 oz. bottles.

Winthrop-Stearns INC.

1450 BROADWAY, NEW YORK 18, N. Y.

Neo-Synephrine Brand of phenylephrine, Thenfadil Brand of dethylondiamine and Zephiran Brand of benzalkonium chloride-refined, trademarks reg. U. S. & Canada

prominent
winter
prescription
for
cough
control

Because **BENYLIN EXPECTORANT** combines Benadryl® hydrochloride with four other established non-narcotic remedial agents physicians know that it can be depended on to provide rapid relief of cough – to liquefy mucous secretions, relax bronchial musculature, soothe irritated mucosae – and also to ease nasal stuffiness, sneezing and lacrimation. From experience many physicians know also that its mildly tart, raspberry taste appeals to children and to adults alike.

BENYLIN EXPECTORANT will be prominent among the prescriptions you fill during the winter season – and now is a good time to check your stock.

BENYLIN® EXPECTORANT

for control of coughs due to colds or allergies

BENYLIN EXPECTORANT contains in each fluidounce:

Benadryl hydrochloride (diphenhydramine hydrochloride, Parke-Davis)	80 mg.	Sodium citrate	5 gr.
Ammonium chloride	12 gr.	Chloroform	2 gr.
		Menthol	1/10 gr.

Packaging: 16-ounce and gallon bottles.

MEDICAMENTA PD CO. PERA

Parke, Davis & Company
DETROIT, MICHIGAN

American Journal of Pharmacy

The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

Former Editors of the Journal have been: Daniel B. Smith, 1825-1828; Benjamin Ellis, 1829-1831; Robert E. Griffith, 1831-1836; Joseph Carson, 1836-1850; William Procter, Jr., 1850-1871; John M. Maisch, 1871-1893; Henry Trimble, 1893-1898; Henry Kraemer, 1898-1917; George M. Beringer, 1917-1921, and Ivor Griffith, 1921-1941.

Established and maintained as a record of the progress of pharmacy and the allied sciences, the Journal's contents and policies are governed by an Editor and a Committee on Publications elected by the members of the College.

Manuscripts should be sent to the Editor, who does not assume any responsibility in connection with the views or investigations of contributors of accepted manuscripts, other than to exercise general care in selection.

Contributors are allowed a reasonable number of copies of this Journal, free of charge, if applied for when the proof is returned.

Reprints, if desired, should be ordered when the proof is returned. The table below shows the *approximate* cost of reprints, the make-up of the pages to be identically the same as in the Journal. The actual cost may vary from the figures given, and will depend upon the amount of presswork, paper, binding, and other factors. Reprints containing half-tones may be expected to cost somewhat more than the rates given.

	2 pp.	4 pp.	8 pp.	16 pp.	Covers with Titles	
50 copies.....	$ 4.50	$10.00	$16.25	$27.50	50 copies.....	$ 7.50
100 "	7.50	13.75	21.25	40.00	100 "	12.50
250 "	10.00	17.50	27.50	53.75	250 "	17.50
500 "	15.00	25.00	35.00	68.75	500 "	26.25

oral penicillin t.i.d.

. . . for the more common bacterial infectious diseases

Just 1 or 2 Pentids Tablets t.i.d. are particularly effective . . . convenient, easy-to-take . . . cause fewer side effects . . . and are less than ½ the cost of the newer antibiotics.

Bottles of 12 and 100.

formulated for convenient t.i.d. dosage **Pentids**

Squibb 200,000 Unit Penicillin Tablets

"PENTIDS" IS A TRADEMARK OF E. R. SQUIBB & SONS

SQUIB

THIS PUBLICATION IS REPRODUCED BY AGREEMENT WITH THE COPYRIGHT OWNER. EXTENSIVE DUPLICATION OR RESALE WITHOUT PERMISSION IS PROHIBITED.